REMARKS/ ARGUMENTS

Applicant has carefully studied the final Examiner's Action mailed November 26, 2008, having a shortened statutory period for response set to expire February 26, 2009. These explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Applicant responds to the outstanding Action by centered headings that correspond to the centered headings employed by Office, to ensure full response on the merits to each finding of Office.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 5-12 and 14-18 stand rejected under 35 USC 103(a) as obvious in light of *Pittenger, et al.* (U.S. Pat. No. 6,387,369), *Erices, et al.* (Br. J. Haematol. 2000, 109, 235-242), *Edelberg, et al.* (P.G. Pub. 2003/0091547) and *Lim, et al.* (Bone Marrow Transpl. 1999, 24, 965-970). The Office found that *Pittenger, et al.* discloses a method of regenerating cardiac muscle with mesenchymal stem cells (MSC), and introduction of MSC to a myocardial infarct reduced the degree of scar formation and augmented ventricular function.[1] The MSC administered by *Pittenger, et al.* may be administered directly or systemically at amounts of 10-40 x 10^6 MSC/ml.[2] The Office noted *Pittenger, et al.* fails to address the administration of umbilical cord blood cells (UCBCs), but found *Erices, et al.* "teach[es] that umbilical cord blood (UCB) is a source for multipotent mesenchymal progenitor cells which differentiate into muscle[.]"[3] The Office concluded that this modification would be obvious because *Edelberg, et al.* provides cardiac myocytes can be differentiated from endothelial precursor cells derived from UCB.[4] Finally, the Office found administering at least 6 million WBC/ml obvious, as discloses that UCB contain about 11 million WBC/ml.[5] Applicant respectfully notes the Office relies on *Lim, et al.* to obviate claims drawn to cell composition concentrations, finding *Lim, et al.* "teach[es] that UCB contains about 11 million white blood cells per ml[.]"[6]

The combination of *Pittenger, et al.*, *Erices, et al.*, and *Edelberg, et al.* does not obviate the claimed invention as fails to address elements of the

[1] Page 3 of the final Office Action, dated Nov. 26, 2008.
[2] Page 4 of the final Office Action, dated Nov. 26, 2008.
[3] *Id.*
[4] *Id.*
[5] Page 6 of the final Office Action, dated Nov. 26, 2008.
[6] Page 6 of the final Office Action, dated November 26, 2008.

claimed invention. In establishing a *prima facie* case of obviousness[7], all words of a claim must be considered.[8]

Claim 1 provides:

> A method of treating a circulatory disorder selected from the group consisting of cardiomyopathy, myocardial infarction, and congenital heart disease, comprising: administering an effective amount of a composition comprising an umbilical cord blood cell to an individual with a circulatory disorder.[9]

The Office contends *Erices, et al.* teaches UCB is a source of mesechymal progenitor cells,[10] and *Pittenger, et al.* teaches introducing mesenchymal stem cells to a cardiac infarct zone.[11] The Office then concluded it was obvious to substitute the MSC for UCB, thereby administering UCB to infarct heart cells.[12] Applicant respectfully brings to the Office's attention *that Erices, et al.* discloses that mesenchymal-like cells (MLCs discussed in *Erices, et al.*) were obtained upon culturing umbilical cord blood cells for over 15 days.[13] These cultured MLCs had the "potential to differentiate into osteoblasts and adipocytes[.]"[14] Thus, *Erices, et al.* concluded these MLCs were some mesenchymal progenitor cell. Moreover, *Pittenger, et al.* uses mesenchymal stem cells (MSC), which are not the MLC cells. *Pittenger, et al.* provides "mesenchymal stem cell compositions are obtained by culturing adherent marrow or periosteal cells[,]"[15] which are sources of adult MSC not UCB-derived MSCs. Implanting these adult MSCs, i.e. bone marrow-derived MSCs, in infarct areas where scar tissue formed results in the formation of more scar tissue.[16] Additionally, the Office has not identified why a skilled artisan would recognize these MLCs are akin to MSCs, and may be used as functional equivalents. Stem cells are different from progenitor cells in that the art considers stem cells to be pluripotent, whereas progenitor cells are multipotent and have undergone some differentiation, thereby limiting the potential of

---

[7] MPEP 2142.
[8] MPEP 2143.03.
[9] Claim 1, as amended in Amendment B, filed February 14, 2008.
[10] Page 4 of the final Office Action, dated November 26, 2008.
[11] Page 3 of the final Office Action, dated November 26, 2008.
[12] Page 4 of the final Office Action, dated November 26, 2008.
[13] Erices, et al., Mesenchymal Progenitor Cells in Human Umbilical Cord Blood, Br. J. Haemat., 109: 235-242, page 238, column 2.
[14] Erices, et al., Mesenchymal Progenitor Cells in Human Umbilical Cord Blood, Br. J. Haemat., 109: 235-242, page 240, column 2; page 241, column 1.
[15] Pittenger, et al. (U.S. 6,387,369), column 2, lines 11-13.
[16] Page 4, paragraph 10 of the Application (citing Wang, et al., 2000 J. Thorac. Cardiovasc. Surg. 120:999-1005).

the cells.[17] "[O]bviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"[18] As such, the combination of *Pittenger, et al.* and *Erices, et al.*, as used by the Office,[19] does not provide a rationale why a skilled artisan would find the claimed invention obvious in light of the references.

Furthermore, the Office found *Erices, et al.*, "teach[es] that umbilical cord blood (UCB) is a source for multipotent mesenchymal progenitor cells which differentiate into muscle[.]"[20] Applicant traverses this finding as *Erices, et al.* discloses that the MLC have the ability to differentiate into osteoblasts and adipocytes,[21] but does not disclose the ability of the cells to differentiate into muscle. *Erices, et al.* does not address the ability of umbilical cord blood cells to form multipotent stem cells. Moreover, *Erices, et al.* fails to discuss the ability of mesenchymal cells to differentiate into cardiac muscle,[22] which is significantly biologically different from skeletal muscle.

The Office also found the claims obvious because *Edelberg, et al.* provides endothelial precursor cells may differentiate into cardiomyocytes, and that these endothelial precursor cells may be derived from UCB. Thus, the Office concluded that a skilled artisan would recognize that the UCB of *Erices, et al.* are a suitable substitute for the MSC disclosed in *Pittenger, et al.*

As stated above, *Erices, et al.* and *Pittenger, et al.* do not teach the claimed invention, as *Erices, et al.* discloses that UCB contains mesenchymal-like cells, which *Erices, et al.* concluded were mesenchymal progenitor cells, not mesenchymal stem cells as used in *Pittenger, et al.*

---

[17] See, Beckmann, et al., Asymmetric cell division within the human hematopoietic stem and progenitor cell compartment: identification of asymmetrically segregating proteins, Blood, **109** (12): 5494–501, page 5494, column 1.
[18] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1741 (2007) (citing *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)).
[19] See, page 4, third full paragraph of the final Office Action, dated November 26, 2008.
[20] Page 4 of the final Office Action, dated November 26, 2008 (citing the entirety of Erices, et al. and specifically page 235, left column).
[21] Erices, et al., Mesenchymal Progenitor Cells in Human Umbilical Cord Blood, Br. J. Haemat., 109: 235-242, page 240, column 2; page 241, column 1.
[22] Cited references: D. Prockop, et al., Marrow Stromal Cells as Stem Cells for Nonhematopoietic Tissues, Science, 276: 71-74, abstract (Stating MSC can form myoblasts*); G. Ferrari, et al., Muscle Regeneration by Bone Marrow-Derived Myogenic Progenitors, Science, 279: 1528-1530, abstract (Discussing the growth and repair of skeletal muscle); P. Conget & Minguell, Phenotypical and Functional Properties of Human Bone Marrow Mesenchymal Progenitor Cells, J. Cell. Physio., 181: 67-73, abstract (Not differentiating between muscle types); M. Pittenger, et al., Multilineage Potential of Adult Human Mesenchymal Stem Cells, Science, 284: 143-147, abstract (Not differentiating between muscle types).
*Myoblast is defined as a cell that gives rise to skeletal muscle cells. http://cancerweb.ncl.ac.uk/cgi-bin/omd?myoblast (last accessed April 22, 2008).

Edelberg, et al. fails to address this shortcoming, as the document discusses endothelial precursor cells, not mesenchymal cells. The Office has not provided a rationale for concluding endothelial precursor cells (EPCs) are mesenchymal stem cells. As noted above, *Edelberg, et al.* focuses on endothelial precursor cells, not the MLCs or MSCs of *Erices, et al.* and *Pittenger, et al.* The Office has not explained why one of skill in the art would conclude that EPCs are similar to MSCs or MLCs, such that *Edelberg, et al.* may be combined with *Erices, et al.* and *Pittenger, et al.* *Lim, et al.* addresses the composition of UCBC, as identified by surface markers,[23] but does not use the markers to determine MSC or EPC. *Lim, et al.* also fails to disclose any correlation between MSCs, MLCs, and EPCs to provide a rationale to support the obviousness rejection. Likewise, *Lim, et al.* fails address the use of umbilical cord blood in treatment of circulatory disorders. As such, the combination fails to teach the administration of UCB or UCB-derived MSC, and fails to teach MSC can differentiate into cardiac muscle, which is required by the rejected claims.

Further, Applicant notes that *Edelberg, et al.* uses myocytes derived from endothelial precursor cells by culturing cells with PDGF.[24] This differs from the present invention, which uses a UCB composition of UCB cells suspended in a carrier such as plasma, fetal bovine serum or DMSO.[25] In specific embodiments, the UCB are isolated mononuclear cells, not endothelial-derived myocytes. Edelberg states PDGF and PDGFR-α are required for allograft survival.[26] However, Edelberg fails to teach the administration of UCB or UCB-derived MSC, and therefore also fails to address the ability of umbilical cord blood cells to form multipotent stem cells.

The combination of *Pittenger, et al.*, *Erices, et al.*, *Edelberg, et al.* and *Lim, et al.* also fails to obviate the claimed invention because the invention discloses unexpected results. The Office found the invention obvious as *Lim, et al.* provides UCB contains approximately 11 million white blood cells.[27] The art recognizes the rarity of MSCs in UCB,[28] with one study finding

---

[23] F. Lim, et al., The Number of Nucleated Cells Reflects the Hematopoietic Content of Umbilical Cord Blood for Transplantation, Bone Marrow Trans. 24:965-970, page 965, column 1 (1999).
[24] Edelberg, et al. (P.G. Pub. 2003/0091547), page 2, paragraph 18.
[25] Page 13, paragraph 41 of the Application.
[26] *Id.* at page 13, paragraph 168.
[27] Page 6 of the final Office Action, dated November 26, 2008.
[28] Kogler, et al., A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential, J. Exp. Med., 2004 Jul 19;200(2):123-35, Astract; Nishiyama, et al., The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro, Stem Cells, 2007 Aug;25(8):2017-24. Epub 2007 May 10, page 2023, column 1, Bieback, et al, Critical parameters for the isolation of

> The UCB-derived MSC-like cells were of clonal origin, because at most one colony developed per well. Therefore the mean (±SD) frequency of MSC-like cells was calculated from all tested UCB units to be 0.7 ±0.2 clone-forming units per 1 x 10^8 MNCs of full-term UCB … and ranges from 0.2 to 2.3 clones per 1 x 10^8 MNCs [.][29]

Pittenger, et al. discloses administering between 20 μl and 50 μl of 10-40 x 10^6 MSC/ml.[30] In an example between 10,000 and 100,000 MSCs were administered to a non-ischemic heart.[31] Adjusting the number of MSC in *Pittenger, et al.* to UCBCs based on *Bieback, et al.*, one would need to administer 1.4 x 10^{12} UCBCs[32] to obtain 10,000 MSCs, the lowest number of MSCs administered to the non-ischemic heart in *Pittenger, et al.* The claimed invention uses between 1 x 10^4 and 5 x 10^7 UCBCs,[33] which is 0.7 x 10^{-8} to 0.35 x 10^{-4} times less than the cells required by *Pittenger, et al.* In comparison, this is between 0.0000007 and 0.0035 percent the number of cells that would be required by *Pittenger, et al.*

Accordingly, it is respectfully requested that Office reconsider claims, 1, 5-12, and 14-18 and withdraw the rejection under 53 U.S.C. § 103(a).

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

---

mesenchymal stem cells from umbilical cord blood, Stem Cell, 2004;22(4):625-34, page 625, column 11 page 626, column 1.

[29] Bieback, et al, Stem Cell 2004;22(4):625-34, page 628, column 1.

[30] Pittenger, et al. (U.S. 6,387,369), column 4, lines 65-67.

[31] Pittenger, et al. (U.S. 6,387,369), column 6, lines 26-33.

[32] 0.7 MSC per 1 x 10^8 MNCs provide (10,000MSC/[0.7 MSC / 1 x10^8 MNC]) = ([10,000MSC/0.7 MSC] x 1 x10^8)

[33] See, page 22, paragraph 74 of the Application.

Very respectfully,

SMITH & HOPEN

/robert varkonyi/

By:_____

Robert Varkonyi
Reg. No. 63,885
180 Pine Avenue North
Oldsmar, Florida 34677
Attorney for Applicant

Dated: February 25, 2009
Customer No. 21,901

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on February 25, 2009.

/lauren reeves/

_____

Lauren Reeves

Date: February 25, 2009